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Sarri, G., Pedder, H., Dias, S., Guo, Y. and Lumsden, M. A. (2017) Vasomotor symptoms resulting from natural menopause: a systematic review and network meta-analysis of treatment effects from the National Institute for Health and Care Excellence guideline on menopause. *BJOG: An International Journal of Obstetrics and Gynaecology*, 124(10), pp. 1514-1523, which has been published in final form at [10.1111/1471-0528.14619](https://doi.org/10.1111/1471-0528.14619). This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

<http://eprints.gla.ac.uk/138525/>

Deposited on: 29 March 2017

Received Date: 08-Jun-2016

Accepted Date: 10-Feb-2017

Article Type: Systematic review

Title: Vasomotor symptoms due to natural menopause; systematic review and network meta-analysis (NMA) of treatment effects from the NICE Menopause Guideline

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Running head: Network meta-analysis of vasomotor symptoms in menopause

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.14619

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Abstract

Background: Vasomotor symptoms (VMS) are the hallmarks of menopause, occurring in approximately 75% of postmenopausal women in the UK and are severe in 25%.

Objectives: To identify which treatments are most clinically effective for the relief of VMS for non-hysterectomized women in natural menopause.

Search Strategy: English publications in MEDLINE, Embase and The Cochrane Library up to 13th January 2015 were searched.

Selection Criteria: Randomized trials (RCTs) of treatments for women with a uterus for the outcomes of frequency of VMS (up to 26 weeks), vaginal bleeding and discontinuation.

Data Collection and Analysis: Bayesian network meta-analysis (NMA) using mean ratios (MRs) and odd ratios (ORs).

Main Results: Across the three networks, 47 RCTs of 16 treatment classes (N=8326 women) were included. When compared to placebo, transdermal oestradiol and progestogen (O+P) had the highest probability of being the most effective treatment for VMS relief (69.8%) (MR: 0.23 [95%CrI (0.09, 0.57)]) whereas oral O+P was ranked lower than transdermal O+P, although oral and transdermal O+P were no different for this outcome (MR: 2.23 [95%CrI (0.7, 7.1)]). Isoflavones and black cohosh were more effective than placebo, though not significantly better than O+P. Not only were SSRIs or SNRIs found ineffective in relieving VMS but they also had significantly higher odds of discontinuation than placebo. Limited data were available for bleeding therefore no conclusions could be made.

Conclusions: For non-hysterectomized women, transdermal O+P was the most effective treatment for VMS relief.

Keywords: menopause, uterus, network meta-analysis, hormonal treatment.

Tweetable abstract: Which treatment best relieves menopause flushes? Results from the #NICE guideline network meta-analysis

Introduction

Menopausal symptoms are extremely common. Vasomotor symptoms (VMS) comprising hot flushes and night sweats are the most common menopausal symptoms occurring in approximately 75% of postmenopausal women, with 25% of these being severely affected in the UK¹. The duration and severity of menopausal symptoms experienced are not uniform – symptoms may develop in the years before the final menstrual period and may persist for a few years or for many years in postmenopause.

Hot flushes often begin as the sudden sensation of heat centred on the upper chest and face. In some instances, this will become generalised, lasting for several minutes, and can be associated with profuse perspiration, palpitations or anxiety which may be very distressing and limit activities of daily living, particularly when they occur repeatedly during the day and at night. At night, hot flushes and night sweats will often cause insomnia that leads to fatigue. The mechanism of VMS appears to involve the central nervous system, possibly due to narrowing of the thermoregulatory-neutral zone in women with hot flushes, associated with instability of the skin blood vessels².

Different treatment options, pharmacological and non-pharmacological, have been used by women to relieve the VMS during menopause. Some of these treatments, such as hormone replacement therapy (HRT) target a “replacement” of oestrogen levels HRT comprises synthetic hormones including oestradiol, conjugated equine oestrogens, oestradiol valerate and several synthetic

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progestogens as well as tibolone which exhibits estrogenic, progestogenic and androgenic effects. Other treatments, such as herbal medicines and psychological therapies may work in different ways. As VMS may resolve naturally, some women simply do not wish to take hormones, while for others HRT is contraindicated, for example women who have (or are at high risk of) hormone-dependent cancer.

We aim to present the evidence obtained via a systematic review (SR), using network meta-analysis (NMA), of pharmacological and non-pharmacological treatments for the relief of VMS, relief of adverse events (such as vaginal bleeding) and discontinuation. This NMA formed part of the evidence underpinned the development of National Institute of Health and Care Excellence (NICE) Menopause Guideline (NG23) (<https://www.nice.org.uk/guidance/ng23>)³. The use of NMA is recommended in healthcare decision making when multiple treatments are considered for one indication and these treatments have not been directly compared in the same trials.

Methods

Systematic Reviews

The protocol of the SR was agreed by the Guideline Development Group (GDG) (Appendix S1), was conducted as part of the development of NICE guideline on menopause (NG23) <https://www.nice.org.uk/guidance/ng23> and is reported according to the PRISMA extension statement for systematic reviews incorporating NMAs of health care interventions⁴. A cost-effectiveness model using results from this NMA, in addition to other evidence, were used by the GDG to make recommendations in the guideline. In summary, the SRs included only randomised controlled trials (RCTs) that assessed pharmacological and/or non-pharmacological treatments for reducing the frequency of VMS, treatment discontinuation and vaginal bleeding for women aged 45

years or older with a diagnosis of natural menopause (defined as amenorrhoea for at least 12 consecutive months).

The population in the NMA protocol was stratified into three groups that formed three networks of connected treatments: women with a uterus, women without a uterus, women with a history or at risk of breast cancer. This paper presents the results of the first network (women with a uterus). For non-oestrogenic treatments we included studies of women without a uterus as their effect was found to be clinically similar. For studies investigating oestrogen plus progestogen we included mixed studies of women with a uterus and without a uterus as long as more than two thirds (66.6%) of the study sample were women with a uterus (Appendix S1).

The efficacy endpoint was the frequency of VMS at the end of treatment, whereas vaginal bleeding and treatment discontinuation were considered measures of adverse events. Although distress caused by VMS may have been an equal relevant outcome for women in menopause, the frequency of VMS was the most commonly reported outcome in studies, and the Guideline Committee highlighted that VMS were highly prevalent among women seeking treatment for menopausal symptoms. Vaginal bleeding and treatment discontinuation were prioritised due to their importance on continuity of healthcare, costs of further treatment, and long-term impact. .

The time points of outcomes recorded were guided by clinical decision on the minimum duration of a trial for the intervention to be effective. Non-hormonal treatments were considered by the GDG to take a minimum of four weeks to be effective, whilst hormonal treatments were considered to take longer (12 weeks). As shorter-term outcomes were the focus of this review, 26 weeks was considered to be the maximum follow-up time we would include, to avoid long-term changes in treatment efficacy that might cause heterogeneity within the network.

All searches were conducted in MEDLINE Embase and The Cochrane Library up to 13th January 2015 restricted to English written articles according to the parameters stipulated within the NICE

Guidelines Manual 2015 (<https://www.nice.org.uk/article/PMG20/chapter/4-Developing-review-questions-and-planning-the-evidence-review>) (Appendix S2). Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Full search strategies were published as part of the full NICE guideline (<http://www.nice.org.uk/guidance/ng23/evidence/appendices-ag-559549262>).

Search strategies were quality assured by cross-checking reference lists of highly relevant papers and comparing with search strategies in other SRs.

Data extraction

Data were double extracted in a structured form using a guide developed by the authors for Data Extraction for Complex Meta-anALysis (DECiMAL) independently by two reviewers⁵⁵. Discrepancies in data extraction were addressed by a senior reviewer who resolved any conflicts.

The quality of the studies was evaluated using two domains (risk of bias, indirectness) of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (<http://www.gradeworkinggroup.org/>)⁶. Detailed results for risk of bias domains are shown in Table S2.

Statistical models

NMA was formulated to synthesise direct and indirect evidence of treatments' effects to reduce the frequency of VMS, treatment discontinuation and vaginal bleeding using the software WinBUGS version 1.4.3. We used statistical models for both fixed and random effects that allowed inclusion of multi-arm trials and accounted for the correlation between arms in the trials with any number of trial arms⁷. A class effect model was selected for the NMA with the underlying assumption that the

effectiveness of different treatments under the same class would be comparable. This decision was made to maximise the availability of data and borrow strength from different trials. Data were available on dosing for many treatments, but the sparseness of the networks meant that it was necessary to borrow strength on dosing within treatments by assuming different doses of the same treatment had the same class effects (fixed effects model (FE)). A model allowing for within-class variability was also assessed to check if it improved model fit and reduced heterogeneity (random effects model (RE)). Two RE models for this were explored: an exchangeable dose effects model, where the pooled relative effects of different treatment doses were assumed to be randomly distributed within each treatment with a common variance (requiring modelling using a second variance parameter); and a fixed dose effects model, where the pooled relative dose effects are assumed equal for all doses of a treatment. For treatments where dosing information was not available, the relative effect at the dose level was assumed to be equal to the treatment effect in both models.

WinBUGS code was adapted from the Dias et al 2011 and is available from the NICE appendices (<https://www.nice.org.uk/guidance/ng23/evidence/appendices-ik-559549264>). The following prior distributions were used:

- Log mean ratios (MRs) in the comparator arms for each study were normally distributed with mean of zero and variance of 1000
- Pooled log MRs at the treatment or class level (depending on model used) were normally distributed with mean of zero and variance of 1000
- Between-study standard deviation followed a uniform distribution between zero and two
- Within-class standard deviation followed a uniform distribution between zero and two

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Placebo was selected as the baseline comparator for all networks as it was the treatment arm most commonly evaluated in RCTs. As no dependency on time was identified in exploratory analyses, discontinuation of treatment and vaginal bleeding were treated as dichotomous outcomes and were modelled on the log-odds ratio scale (Figure S2). Exploratory analyses also showed that baseline frequency of VMS followed an overdispersed Poisson distribution thus it was not appropriate to use a standard Poisson distribution to model the frequency of VMS (Figure S3). The negative binomial distribution can be used to model an overdispersed Poisson distribution, by including a parameter that accounts for the overdispersion^{8,9,10}. The mean of this negative binomial is interpreted as the rate of the over-dispersed Poisson and can be approximated by a normal distribution. We therefore model the mean using a log link function and relative treatment effects are estimated as log-mean ratios. Our motivation was to model data as closely as possible to the mechanism by which they were generated (i.e. from an overdispersed Poisson distribution) and this approximation provided a simple computational solution whilst retaining the interpretation of the pooled effect as mean rates of VMS

On the log mean ratio scale, final and change from baseline frequencies of VMS could not be pooled, so the latter was transformed so that all effects could be modelled as final frequencies. A correlation coefficient of 0.55 was used to estimate final frequencies from change from baseline. This was calculated from two included studies which reported baseline, final and change from baseline results in full^{11,12}.

All three models (FE, RE with fixed dose effects, RE with exchangeable dose effects) were compared based on residual deviance and deviance information criteria (DIC)^{7,13}. Between-studies heterogeneity estimates from random effects models are presented as median and 95% credible intervals (95%CrI).

Inconsistency in the networks was tested in closed loops of treatment comparisons by node-splitting¹⁴. This technique allows the splitting of direct and indirect information contributing to each

treatment effect. The difference between these contributions can be statistically tested, with a rejection of the null hypothesis indicating significant inconsistency in the network.

The output of the NMA was expressed as the probability of each treatment being the best for an outcome (based on the proportion of Markov chain simulations in which a treatment ranked first) and the ranking of treatments (presented as median rank and its 95%CrI). The estimation of summary estimates (mean ratios [MRs] or odds ratios [ORs]) were also calculated for comparisons of the direct and indirect evidence using medians and 95%CrIs from the posterior distributions.

Two types of sensitivity analyses were predefined in the NMA protocol. The first focused on changing the value of the correlation coefficient used to estimate final frequencies of VMS from change from baseline, from 0.55 in the original analysis to a typically assumed correlation between baseline and follow-up of 0.75. The second analysis tested if differences in treatment efficacy could be explained by differences in dosing. Studies investigating the treatment of low dose oral oestradiol plus progestogen were removed from the analysis to determine if this dose was reducing the overall efficacy of oral oestradiol plus progestogen in the model. The final results were not found to be sensitive to either of these changes.

A further post-hoc sensitivity analysis was considered to investigate the effect of including mixed population studies (women with and without a uterus) of oestrogen plus progestogen. However, as there was only a single study³² that included mixed populations for this treatment comparison, exclusion of the study removed oestrogen plus progestogen oral from the network and prevented estimation of the efficacy of this treatment. No other results were affected by the exclusion of this study.

Results

47 RCTs matched the protocol, presented information for at least one of the outcomes and were included in the NMA (Figure S1). For the two first networks (frequency of VMS and discontinuation of treatment), DIC suggested that there was a small difference between any of the models (differences less than 5 points are not considered meaningful) (Tables S7). However, the residual deviance for the random effects model with fixed dose effects for both these networks was slightly closer to the number of unconstrained data points than either of the other models (for the fixed effects and random effects with exchangeable dose effects respectively). Therefore, the results of the random effects model with fixed dose effects are presented for these two networks. For the network of vaginal bleeding, the results of the fixed effects model are presented, as the estimate of heterogeneity for the random effects model was unstable, and strongly influenced by the prior distribution.

a. Reducing the frequency of VMS

A total of 32 RCTs of 12 treatment classes (placebo, sham acupuncture, oestrogen plus progestogen non-oral, oestrogen plus progestogen oral, tibolone, raloxifene, SSRIs/SNRIs, isoflavones, Chinese herbal medicine, black cohosh, multibotanicals, acupuncture) with a sample size of 4165 women were included for the NMA for VMS (Figure 1, Table S1). Two included RCTs was at very high risk of bias and 13 were high risk (Table S2). The other 21 RCTs were low or moderate risk. The combination of oestrogen plus progestogen via patches was found to be better than placebo (MR 0.23 95%CrI (0.09, 0.57)) at relieving VMS for women in menopause and had the highest probability of being the best treatment (68.9%) (Figure 2A, Table 1). Although, the 95%CrI for combination of oral oestrogen plus progesterone compared to placebo was wide (MR 0.52 (0.25, 1.06)), the point estimate suggested that it may have good efficacy, similar to that of transdermal oestrogen plus progestogen.

In addition, there was strong evidence to suggest that the combination of oestrogen plus progestogen via patches was more effective than raloxifene, SSRIs/SNRIs, isoflavones and Chinese herbal medicine in relieving VMS. Isoflavones and black cohosh were also found to be better than placebo. There was no strong evidence of any other effects among other interventions in the network (Table S3).

High heterogeneity was found between studies, reducing the precision of estimates. This is likely to have arisen because of the clinical differences in patients included in the studies – the baseline frequency of hot flushes varied considerably between studies. Inconsistency was assessed in the closed loop between placebo, sham acupuncture and acupuncture, but no difference was found between results obtained through direct and indirect evidence (Table S3).

a. Treatment discontinuation

A total of 21 RCTs of 10 treatment classes (placebo, oestrogen plus progestogen oral, conjugated oestrogens plus bazedoxifene, tibolone, SSRIs/SNRIs, gabapentin, isoflavones, Chinese herbal medicine, multibotanicals, valerian root) with a sample size of 4829 women were included in the network for discontinuation of treatment (Figure 1, Table S1). Because of high heterogeneity between the studies included in the NMA, uncertainty of the results was increased. Inconsistency could not be assessed in this network as there were no closed-treatment loops. Only 4 RCTs were at high risk of bias. The other 17 were low or moderate risk (Table S2). There was evidence that the combination of non-oral oestrogen plus progestogen had significantly lower odds of discontinuation than placebo (OR 0.61 95%CrI (0.37, 0.99)). In addition, there was evidence that conjugated oestrogens plus bazedoxifene (OR 0.31 95%CrI (0.1, 1.00)) was more effective than placebo in this outcome, although there was considerable uncertainty in this result. There was strong evidence that SSRIs/SNRIs were worse than placebo (OR 1.66 95%CrI (1.07, 2.61)) on discontinuation of treatment.

There was evidence that Tibolone and SSRIs/SNRIs were worse than non-oral oestrogen plus progestogen and conjugated oestrogens plus bazedoxifene for this outcome (Figure 2B, Table 2, Table S4).

In this analysis, conjugated oestrogens plus bazedoxifene and valerian root were found to have the highest probability (37.34% and 37% respectively) of being the best treatments in relation to discontinuation of treatment among interventions with duration up to 26 weeks, although note that these probabilities are small and below 50%

a. Vaginal bleeding

The network of vaginal bleeding included five RCTs of 5 treatment classes (placebo, oestrogen plus progestogen oral, tibolone, SSRIs/SNRIs, gabapentin) (Figure 1, Table S1) with a sample size of 1367 women. Neither heterogeneity nor inconsistency could be assessed in the network due to its sparseness. A fixed effects model was used and there were no closed-treatment loops. One study was at high risk of bias, one was low risk, and the other three were moderate risk (Table S2). The sparseness of data within the network meant that there was a high degree of uncertainty in estimates, and no conclusions could be drawn regarding effects of treatments on vaginal bleeding (adverse event) (Figure 2C, Table S5, Table S6).

Discussion

This paper summarizes the evidence included in three SRs and analysed in NMAs for the outcomes of relief of frequency of VMS, treatment discontinuation and vaginal bleeding among pharmacological and non-pharmacological treatments for women with a uterus who have

undergone a natural menopause. To our knowledge, this is the first publication using this type of complex analysis in the research field of menopause.

Main findings

NMA results showed that for women with a uterus, the oestrogen plus progestogen transdermal patch was the most effective treatment to relieve the frequency of VMS, with a lower odds of discontinuation compared with all the other available treatments (hormonal, non-hormonal and non-pharmacological). There was evidence that oestrogen plus progestogen taken orally may be more effective to relieve VMS than placebo, but this did not rank as highly as transdermal oestrogen plus progestogen in the hierarchy of the best treatment options for this outcome. However, in the clinical setting both may be considered as options, depending on the individual's response to treatment. Although isoflavones and black cohosh, were also shown to be more effective than placebo in relief of VMS for women with a uterus, there was no evidence that their efficacy differed from combined oestrogen plus progestogen. However, these results should be interpreted with caution as there was a variety of herbal preparations used in different studies. SSRIs/SNRIs were not found to be effective in relieving VMS but were found to have higher odds of discontinuation compared to the other treatments, as would be expected due to the serious side effects profile of these treatments. However, the NMA demonstrated that women treated with non-oral oestradiol plus progestogen or with conjugated oestrogens plus bazedoxifene were less likely to discontinue treatment than if they were treated with placebo or tibolone.

No conclusive points could be made for the outcome of vaginal bleeding for women with a uterus given the limited data for this outcome and the lack of inclusion of several interventions in the network.

During the NICE guideline development, results of clinical efficacy from the NMA were incorporated into a probabilistic cost-effectiveness analysis that informed the decision-making of the Guideline

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Committee. The Committee concluded that women with a uterus should be offered the treatment of oestrogen and progestogen (HRT) for the relief of VMS, following an individualized approach and after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. Health professionals should not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for VMS alone and should explain to women that although there is some evidence that isoflavones or black cohosh may relieve VMS there are health concerns in relation to safety of multiple preparations and interactions with other medicines (<https://www.nice.org.uk/guidance/ng23/>)

Strengths and Limitations

This is the first NMA designed to include simultaneous comparison of randomized evidence aiming to reduce the frequency of VMS for women in menopause. Advanced statistical techniques were employed to make best use of available evidence. A novel NMA model which accounts for the nature of the VMS data, distributed as overdispersed Poisson, and incorporates class effects and transformation of change from baseline scores of outcomes, was developed to make use of as much relevant and available data as possible. We were therefore simultaneously able to compare several interventions of interest to women and policy makers that had not been compared previously in head-to-head trials.

Overall there were relatively few studies included in the networks compared to the number of treatment comparisons. This may have led to the within-class standard deviation parameter not being fully informed, which could explain the better fit of the fixed dose effect RE model compared to the exchangeable dose effect RE model. A dose-response relationship might have been expected in the data, but as the protocol specified that treatments had to be administered within selective doses specified in the British National Formulary, the range of doses was often very small.

Furthermore, body weights and absorption can vary substantially between patients, and this is likely to lead to as much (if not more) variation in bioavailability of treatment than the administered dose.

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Several decisions were made at the protocol stage that impacted the selection of data included in the networks and therefore the representativeness of all available evidence in this area. For example, we included only English-published studies, which may have limited our evidence on some treatments (e.g. Chinese herbal medicines), and publication bias was not easily assessed. Furthermore, it was decided to examine the role of different treatments used to reduce the frequency rather than the severity of VMS, which resulted in some treatments such as cognitive behaviour therapy being excluded from the NMA. The selection of outcomes for inclusion in the NMA was based on both their clinical importance and relevance to women in menopause. Frequency of VMS, discontinuation and vaginal bleeding were prioritised for inclusion due to their high prevalence and availability of evidence.

Assumptions were also made for the minimum duration of trials for inclusion in the NMA and the minimum acceptable criteria for mixed population studies. These assumptions are commonly made when a complex meta-analysis is designed and aim to increase the homogeneity and validity of included data. However, this resulted in a number of studies being excluded from further analysis. Some studies were also excluded because the data reported did not give an indication of variability (no information on standard deviation or standard error of results). For the small minority of studies that were excluded because they did not connect to the network, their results and whether they would influence decision-making were further discussed with the GDG. This information was used as supplementary evidence to facilitate the Group's discussion which recognised the importance of these treatments in the management of some women with menopause, especially if they do not wish to be treated with pharmacological treatments (such as HRT) and these options were highlighted in terms of provision of general advice and information.

Interpretation

This is the first NMA designed to include simultaneous comparison of randomized evidence from pharmacological and non-pharmacological treatments aiming to reduce the frequency of VMS for women in menopause. After taking into account the assumptions used for this NMA and the limitations of this approach, these results provided a comprehensive framework for decision making by combing direct and indirect evidence on treatments for the relief of VMS in menopause. Our reviewed literature did not identify any other similar type of analysis that could be used for our results comparison.

Conclusions

There is evidence that transdermal oestradiol plus progestogen greatly reduces the frequency of hot flushes in women with a uterus. Although there is some evidence of efficacy of oral oestrogen plus progestogen treatment, the health economic analysis and the GDG's expert opinion supported the use of both types of oestradiol plus progestogen's administration in clinical practice.

Acknowledgements

The authors thank Nichole Taske (NICE Director for Methodology) for providing valuable comments on earlier versions of this paper.

Disclosure of interests

We declare the following interests based on NICE's policy on conflicts of interests (available at: www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/code-of-practicefor-declaring-and-managing-conflicts-of-interest.pdf). MAL has been remunerated for chairing NICE guideline development committees and is vice chair of the Women's Health Expert Advisory Group

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to the Medicines and Healthcare products Regulatory Agency (MHRA). SD is co-investigator on an MRC/Pfizer collaboration grant in which Pfizer part-fund a researcher (not SD). GS, HP and YG have no conflicts of interest to declare. ICMJE disclosure forms are available as online supporting information.

Contributions to authorship

GS has prepared the first draft of the publication and was responsible for revisions and ensuring overall integrity of the process. All co-authors (GS, HP, YG, SD, MAL) contributed to reviews and approved the final version of the manuscript.

Funding

This work was undertaken in part by authors (GS, HP, YG) from the National Guideline Alliance (formerly the National Collaborating Centre for Women and Children's Health) which received funding from the National Institute for Health and Care Excellence. The views expressed in this publication are those of the authors and not necessarily those of the Institute.

SD received support from the Centre for Clinical Practice (NICE), with funding from the NICE Clinical Guidelines Technical Support Unit, University of Bristol and from the Medical Research Council (MRC Grant MR/M005232/1)

References

1. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015; 175:531-9.
2. Sassarini J, Fox H, Ferrell W, Sattar N, Lumsden MA. Hot flushes, vascular reactivity and the role of the adrenergic nervous system. *Climacteric Aug* 2012; 15:332-8.

- Accepted Article
3. National Institute for Health and Care Excellence. Menopause: diagnosis and management (Clinical guideline23) 2015. <https://www.nice.org.uk/guidance/ng23>.
 4. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162:777-84.
 5. Pedder HP, Sarri G, Keeney E, Nunes V, Dias S. Data Extraction for Complex Meta-Analysis (DECIMAL) Guide. *Syst Rev* 2016; 5:212.
 6. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924-6
 7. Dias S, Sutton AJ, Ades AE, Welton NJ Evidence Synthesis for Decision Making 2: A generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013; 33:607-17.
 8. Mccullagh P, Nelder JA. *Generalised Linear Models 2nd edition*. London: Chapman and Hall, 1989.
 9. Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. *The BUGS book*. Boca Raton: Talor & Francis Inc, 2013.
 10. Martina R, Kay R, van Maanen R, Ridder A. The analysis of incontinence episodes and other count data in patients with overactive bladder by Poisson and negative binomial regression. *Pharm Stat* 2014; 14:151-60.
 11. Faure ED, Chantre P, Mares P. Effects of a standardised soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 2002; 9:329-34.

- Accepted Article
12. Lin SQ, Sun LZ, Lin JF, Yang X, Zhang LJ, Qiao J, et al. Estradiol 1 mg and drospirenone 2 mg as hormone replacement therapy in postmenopausal Chinese women. *Climacteric* 2011; 14:472-81.
 13. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Series B Stat Methodol* 2002; 64:583-616.
 14. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010; 29:932-44.
 15. Al-Azzawi F, Wahab M, Habiba M, Akkad A, Mason T. Continuous combined hormone replacement therapy compared with tibolone. *Obstet and Gynecol* 1999; 93:258-64.
 16. Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flushes. *Obstet Gynecol* 1998; 91:6-11.
 17. Baber RJ, Templeman C, Morton T, Kelly GE, West L. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. *Climacteric* 1999; 2:85-92.
 18. Burke GL, Legault C, Anthony M, Bland DR, Morgan TM, Naughton MJ, et al. Soy protein and isoflavone effects on vasomotor symptoms in peri- and postmenopausal women: the Soy Estrogen Alternative Study. *Menopause* 2003; 10:147-53.
 19. D'Anna R, Cannata ML, Marini H, Atteritano M, Cancellieri F, Corrado F, et al. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 2-year randomized, double-blind, placebo-controlled study. *Menopause* 2009; 16:301-6.
 20. Endrikat J, Graeser T, Mellinger U, Ertan K, Holz C. A multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the efficacy of a continuous-combined hormone therapy preparation containing 1mg estradiol valerate/2mg dienogest on hot flushes in postmenopausal women. *Maturitas* 2007; 58:201-7.

21. Evans M, Elliott JG, Sharma P, Berman R, Guthrie N. The effect of synthetic genistein on menopause symptom management in healthy postmenopausal women: a multi-center, randomized, placebo-controlled study. *Maturitas* 2011; 68:189-96.
22. Faure ED, Chantre P, Mares P. Effects of a standardized soy extract on hot flashes: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 2002; 9:329-34.
23. Ferrari A. Soy extract phytoestrogens with high dose of isoflavones for menopausal symptoms. *J Obstet Gynaecol Res* 2009; 35:1083-90.
24. Freedman RR. Treatment of menopausal hot flashes with 5-hydroxytryptophan. *Maturitas* 2010; 65:383-5.
25. Freedman RR, Kruger ML, Tancer ME. Escitalopram treatment of menopausal hot flashes. *Menopause* 2011; 18:893-96.
26. Freeman EW, Guthrie KA, Caan B, Sternfeld B, Cohen LS, Joffe H, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA* 2011; 305: 267-74.
27. Garcia JT, Gonzaga F, Tan D, Ng TY, Oei PL, Chan CW. Use of a multibotanical (Nutrafem) for the relief of menopausal vasomotor symptoms: a double-blind, placebo-controlled study. *Menopause* 2010; 17:303-8.
28. Gordon PR, Kerwin JP, Boesen KG, Senf J. Sertraline to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general population. *Menopause* 2006; 13:568-75.
29. Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF. Ineffectiveness of sertraline for treatment of menopausal hot flashes: a randomized controlled trial. *Obstet Gynecol* 2007; 109:823-30.
30. Guttuso T Jr, Kurlan R, McDermott MP, Kiebertz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003; 101:337-45.

31. Hachul H, Brandão LC, D'Almeida V, Bittencourt LR, Baracat EC, Tufik S. Isoflavones decrease insomnia in postmenopause. *Menopause* 2011; 18:178-84.
32. Hammar ML, van de Weijer P, Franke HR, Pornel B, von Mauw EM, Nijland EA. Tibolone and low-dose continuous combined hormone treatment: vaginal bleeding pattern, efficacy and tolerability. *BJOG* 2007; 114:1522-9.
33. Joffe H, Guthrie KA, LaCroix AZ, Reed SD, Ensrud KE, Manson JE, et al. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. *JAMA Intern Med* 2014; 174:1058-66.
34. Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss HB. Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *Breast J* 2006; 12:114-22.
35. Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. *Climacteric* 1999; 2:79-84.
36. Knight DC, Howes JB, Eden JA, Howes LG. Effects on menopausal symptoms and acceptability of isoflavone-containing soy powder dietary supplementation. *Climacteric* 2001; 4:13-8.
37. Landgren MB, Helmond FA, Engelen S. Tibolone relieves climacteric symptoms in highly symptomatic women with at least seven hot flushes and sweats per day. *Maturitas* 2005; 50:222-30.
38. Lin SQ, Sun LZ, Lin JF, Yang X, Zhang LJ, Qiao J, et al. Estradiol 1 mg and drospirenone 2 mg as hormone replacement therapy in postmenopausal Chinese women. *Climacteric* 2011; 14:472-81.
39. Lipovac M, Chedraui P, Gruenhut C, Gocan A, Kurz C, Neuber B, et al. The effect of red clover isoflavone supplementation over vasomotor and menopausal symptoms in postmenopausal women. *Gynecol Endocrinol* 2012; 28:203-7.
40. Mirabi P, Mojab F. The effects of valerian root on hot flashes in menopausal women. *Iran J Pharm Res* 2013; 12:217-22.

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41. Nedeljkovic M, Tian L, Ji P, Déglon-Fischer A, Stute P, Ocon E, et al. Effects of acupuncture and Chinese herbal medicine (Zhi Mu 14) on hot flushes and quality of life in postmenopausal women: results of a four-arm randomized controlled pilot trial. *Menopause* 2014; 21:15-24.
 42. Nir Y, Huang MI, Schnyer R, Chen B, Manber R. Acupuncture for postmenopausal hot flashes. *Maturitas* 2007; 56:383-95.
 43. Notelovitz M, Lenihan JP, McDermott M, Kerber IJ, Nanavati N, Arce J. Initial 17beta-estradiol dose for treating vasomotor symptoms. *Obstet Gynecol* 2000; 95:726-31.
 44. Palacios S, Farias ML, Luebbert H, Gomez G, Yabur JA, Quail DC, et al. Raloxifene is not associated with biologically relevant changes in hot flushes in postmenopausal women for whom therapy is appropriate. *Am J Obstet Gynecol* 2004; 191:121-31.
 45. Panay N, Ylikorkala O, Archer DF, Gut R, Lang E. Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief. *Climacteric* 2007; 10:120-31.
 46. Penotti, M., Fabio, E., Modena, A.B., Rinaldi, M., Omodei, U., Viganó, P. (2003) Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries, *Fertility and Sterility*, 79: 1112-1117.
 47. Penotti M, Fabio E, Modena AB, Rinaldi M, Omodei U, Viganó P. Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertil Steril* 2003; 79:1112-7.
 48. Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. *Menopause* 2009; 16:1116-24
 49. Pinkerton JV, Constantine G, Hwang E, Cheng RF; Study 3353 Investigators. Desvenlafaxine compared with placebo for treatment of menopausal vasomotor symptoms: a 12-week, multicenter, parallel-group, randomized, double-blind, placebo-controlled efficacy trial. *Menopause* 2013; 20:28-37.

50. Pinkerton JV, Kagan R, Portman D, Sathyanarayana R, Sweeney M; Breeze 3 Investigators. Phase 3 randomized controlled study of gastroretentive gabapentin for the treatment of moderate-to-severe hot flashes in menopause. *Menopause* 2014; 21:567-73.
51. Rotem,C., Kaplan,B. (2007) Phyto-Female Complex for the relief of hot flushes, night sweats and quality of sleep: randomized, controlled, double-blind pilot study, *Gynecological Endocrinology*, 23: 117-122.
52. Rotem C, Kaplan B. Phyto-Female Complex for the relief of hot flushes, night sweats and quality of sleep: randomized, controlled, double-blind pilot study. *Gynecol Endocrinol* 2007; 23:117-22.
53. Schurmann,R., Holler,T., Benda,N. (2004) Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens, *Climacteric*, 7: 189-196.
54. Schürmann R, Holler T, Benda N. Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric* 2004; 7:189-96.
55. Shahnazi M, Nahae J, Mohammad-Alizadeh-Charandabi S, Bayatipayan S. Effect of black cohosh (*cimicifuga racemosa*) on vasomotor symptoms in postmenopausal women: a randomized clinical trial. *J Caring Sci* 2013; 2:105-13.
56. Speroff,L., Whitcomb,R.W., Kempfert,N.J., Boyd,R.A., Paulissen,J.B., Rowan,J.P. (1996) Efficacy and local tolerance of a low-dose, 7-day matrix estradiol transdermal system in the treatment of menopausal vasomotor symptoms, *Obstetrics and Gynecology*, 88: 587-592,
57. Speroff L, Whitcomb RW, Kempfert NJ, Boyd RA, Paulissen JB, Rowan JP. Efficacy and local tolerance of a low-dose, 7-day matrix estradiol transdermal system in the treatment of menopausal vasomotor symptoms. *Obstet Gynecol* 1996; 88:587-92.
58. Stearns,V., Beebe,K.L., Iyengar,M., Dube,E. (2003) Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial, *JAMA*, 289: 2827-2834.

59. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003; 289:2827-34.
60. Stevenson JC, Durand G, Kahler E, Pertyński T. Oral ultra-low dose continuous combined hormone replacement therapy with 0.5 mg 17 β -oestradiol and 2.5 mg dydrogesterone for the treatment of vasomotor symptoms: results from a double-blind, controlled study. *Maturitas* 2010; 67:227-32.
61. van de Weijer PH, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* 2002; 42:187-93.
62. Verhoeven MO, van der Mooren MJ, van de Weijer PH, Verdegem PJ, van der Burgt LM, Kenemans P, et al. Effect of a combination of isoflavones and *Actaea racemosa* Linnaeus on climacteric symptoms in healthy symptomatic perimenopausal women: a 12-week randomized, placebo-controlled, double-blind study. *Menopause* 2005; 12:412-20.
63. Wyon Y, Wijma K, Nedstrand E, Hammar M. A comparison of acupuncture and oral estradiol treatment of vasomotor symptoms in postmenopausal women. *Climacteric* 2004; 7:153-64.
64. Xia Y, Zhao Y, Ren M, Zhang J, Wang Y, Chang Y, et al. A randomized double-blind placebo-controlled trial of a Chinese herbal medicine preparation (Jiawei Qing'e Fang) for hot flashes and quality of life in perimenopausal women. *Menopause* 2012; 19:234-44.
65. Zaborowska E, Brynhildsen J, Damberg S, Fredriksson M, Lindh-Astrand L, Nedstrand E, Wyon Y, Hammar M. (2007) Effects of acupuncture, applied relaxation, estrogens and placebo on hot flushes in postmenopausal women: an analysis of two prospective, parallel, randomized studies, *Climacteric*, 10: 38-45.
66. Zaborowska E, Brynhildsen J, Damberg S, Fredriksson M, Lindh-Astrand L, Nedstrand E, et al. Effects of acupuncture, applied relaxation, estrogens and placebo on hot flushes in postmenopausal women: an analysis of two prospective, parallel, randomized studies. *Climacteric* 2007; 10:38-45.

67. Zhong LL, Tong Y, Tang GW, Zhang ZJ, Choi WK, Cheng KL, et al. A randomized, double-blind, controlled trial of a Chinese herbal formula (Er-Xian decoction) for menopausal symptoms in Hong Kong perimenopausal women. *Menopause* 2013; 20:767-76.

Table 1: Log mean ratios (with their 95% CI) of all interventions in the network and the probability of being the best treatment for reducing the frequency of VMS

	Median log mean ratios	95%CrI	Probability of being the best treatment	Median (95% CrI) treatment rank
Placebo	Reference treatment		0.00%	10 (7-12)
Sham acupuncture	-0.30	(-1.32, 0.64)	1.44%	7 (2-12)
Oestrogen + progestogen non-oral	-1.46	(-2.37, -0.56)	69.82%	1 (1-5)
Oestrogen + progestogen oral	-0.67	(-1.4, 0.06)	3.73%	4 (1-10)
Tibolone	-0.60	(-1.45, 0.25)	4.02%	5 (1-11)
Raloxifene	0.50	(-0.49, 1.51)	0.04%	12 (6-12)
SSRIs/SNRIs	-0.17	(-0.61, 0.26)	0.01%	8 (4-11)
Isoflavones	-0.48	(-0.82, -0.13)	0.10%	6 (3-9)
Chinese herbal medicine	-0.05	(-0.78, 0.63)	0.09%	9 (4-12)
Black cohosh	-0.92	(-1.8, -0.11)	14.23%	3 (1-9)
Multibotanicals	-0.34	(-1.43, 0.73)	2.88%	7 (1-12)
Acupuncture	-0.54	(-1.49, 0.31)	3.64%	5 (1-11)

Between-study heterogeneity: Standard deviation on the log MRs scale (SD) (95% CrI) 0.50 (0.37, 0.70)

Table 2: Log odd ratios (with their 95% CrI) of all interventions in the network and the probability of being the best treatment for discontinuation of treatment

	Median log odds ratios	95%CrI	Probability of being the best treatment	Median (95% CrI) treatment rank
Placebo	Reference treatment		0.00%	6 (4-8)
Oestrogen + progestogen oral	-0.50	(-0.99, -0.01)	2.83%	3 (1-6)
Conjugated oestrogens plus bazedoxifene	-1.16	(-2.28, 0.002)	37.34%	2 (1-6)
Tibolone	1.73	(-0.06, 5.15)	0.03%	10 (6-10)
SSRIs/SNRIs	0.50	(0.06, 0.96)	0.00%	8 (6-10)
Gabapentin	-0.13	(-0.46, 0.21)	0.08%	5 (3-8)
Isoflavones	-0.05	(-0.67, 0.57)	0.29%	6 (2-9)
Chinese herbal medicine	0.46	(-0.86, 1.9)	0.66%	8 (2-10)
Multibotanicals	-0.70	(-2.63, 1.51)	21.77%	3 (1-10)
Valerian root	-0.91	(-4.41, 1.69)	37.00%	2 (1-10)

Between-study heterogeneity: Standard deviation on the log MRs scale (SD) (95% CrI) 0.25 (0.01, 0.70)



